

50th Anniversary Historical Article

The Framingham Offspring Study: A Commentary

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This historic article review addressing several articles, including P. W. Wilson et al.'s seminal 1980 article on the Framingham Offspring Study, clearly demonstrates how the Framingham Heart Study was a true milestone in the history of cardiology.

prevalence of atherosclerotic vascular disease was appreciated, and its primary relation to sudden death, myocardial infarction and stroke recognized. From this realization came an understanding of the potential for the serious personal, economic and political consequences of atherosclerotic vessel disease (ASVD) and the identification of ASVD as a

Prevalence of Coronary Heart Disease in the Framingham Offspring Study: Role of Lipoprotein Cholesterols

by P. W. Wilson, R. J. Garrison, W. P. Castelli, M. Feinleib, P. M. McNamara, and W. B. Kannel (6)

ABSTRACT

Forty-three of 1,312 men aged 35 to 54 years in the Framingham Offspring Study had clinically recognized coronary heart disease at the initial examination. Twenty-six men in this group had previously had a myocardial infarction. Of 1,296 women in the same age range, only 11 had coronary disease and 3 a prior myocardial infarction. The prevalence of coronary heart disease in men was strongly associated with age, smoking, high density lipoprotein (HDL), low density lipoprotein (LDL) and total cholesterol using univariate analyses. When multivariate logistic regression analysis was used, age, smoking and HDL and LDL cholesterol retained their significant association with coronary heart disease. The total cholesterol/HDL cholesterol ratio was also strongly associated with coronary heart disease in the multivariate analysis. It is concluded that both HDL and LDL cholesterol are strongly and independently associated with the prevalence of coronary heart disease, whereas the level of very low density lipoprotein cholesterol makes no statistically significant independent contribution.

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Review

In the late 1940s, a longitudinal observational overview—the Framingham Heart Study—was organized and funded by grants from the National Heart Institute (1). This study was launched after World War II, when the alarming

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INTRODUCTION

In this edition of the Journal, we release the fifth in a series of reviews of influential articles that have been previously published in ACC journals, including the *American Journal of Cardiology* (from 1958 to 1982) and *JACC* (from 1983 to the present). The publication of these articles is only one aspect of the ACC's 50th anniversary commemoration, which highlights 50 years of leadership in cardiovascular care and education. The articles are intended to encourage reflection on the remarkable progress made in cardiovascular medicine over time, as well as to acknowledge the amazing prescience of some early investigators in anticipating and, in many cases, later guiding developments in their field.

The working group responsible for selecting these articles and asking reviewers to write editorials solicited suggestions from the ACC's clinical committees and individual members.

The group achieved consensus fairly easily, including whom the group should ask to prepare the accompanying editorials. We initially drew up a list of 14 general areas to cover in this series, but later found that there are several major areas of modern cardiology, prominently molecular cardiology, in which the truly landmark articles have, alas, not yet been published in *JACC*. Therefore, the working group decided not to categorize by subject, but instead, to concentrate on the most important articles.

The working group, a task force of the Subcommittee for the Commemoration of the ACC 50th Anniversary, owes a great deal to Ms. May A. Roustom and the efficient and tireless staff at Heart House for facilitating this project. We also wish to thank all who suggested articles and, most important, the authors who prepared reviews for their willingness to contribute their time and wisdom.

Influential Articles in JACC Working Group

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national concern. To better define the prevalence, demography and correlates of atherosclerosis required a comprehensive epidemiologic survey of the disorder and associated or causative factors. Initially, it was thought that a single general etiology for atherosclerotic disease would be found; it is now clear that atherosclerosis and its complications must be considered as both polygenic and multifactorial.

In a recent article titled "Unlocking the Heart's Secrets," *U.S. News and World Report* (Sept. 7, 1998) (2) declared, "The Framingham Heart Study is one of the most celebrated works of epidemiology in the history of medicine." Dr. M. E. DeBakey commented, "It has set the model in epidemiology. . . . It is truly one of the great studies of this century."

It is generally agreed that the Framingham Heart Study has provided information critical to the recognition and management of atherosclerosis and its secular causes and complications. In the near future, new knowledge of the polygenic background of these vascular disorders and their fundamental biology, identification of "genetic" protection against, or propensity for, those biologic mechanisms and responses that underlie arterial wall pathology, and thrombotic responses to injury will provide a further paradigm shift in the understanding of atherosclerosis.

Regrettably, common use of terms from authoritative lay dictionaries without regard for actual medical definitions has irrevocably established the terms "prevention," "primary," and "secondary" in this field. "Prevention," for example, is defined in Webster (3) as follows: "1. To keep from occurring, 2. to stop from doing something, 3. to interpose a hindrance." To "prevent," therefore, is to stop something by forestalling action and rendering it impossible. This desired outcome—the elimination of atherosclerotic vascular disease by current strategies—is currently improbable in all but a few individuals who are genetically fortunate. In contrast, to "hinder" is to hold back by delaying or stopping progress or action; this term is more appropriate for current accomplishments. True prevention will require solution of the second component of the problem—the genetic predisposition or susceptibility to vascular disease or the protection against the influence of secular factors known and unknown. Genetics govern cellular and system responses. Some persons may have "healthy" endothelium, and others may have a thrombotic overresponse. These opposite and complex mechanisms are essential targets for future research that might permit true prevention.

THE FRAMINGHAM HEART STUDY

For the first collection of community cohort information, 1,980 men and 2,421 women were enrolled between 1948 and 1951 (4). Historical data collected sought evidence for prior coronary heart disease (CHD) and specifics regarding blood pressure elevation, smoking habits and alcohol use were also included. A physical examination was conducted and an electrocardiogram obtained. Laboratory values, in-

cluding serum lipoprotein cholesterol levels, were obtained by standardized methods, but values of high-density lipoprotein cholesterol (HDL-C) were not measured in all subjects. The resulting seminal article, "Factors of Risk in the Development of Coronary Heart Disease: Six-Year Follow-up Experience. The Framingham Heart Study" was published in the *Annals of Internal Medicine* in 1961. From this article, the concept of "risk factors" was elaborated upon and the development of a cardiovascular risk profile emerged (5-7).

The Framingham Offspring Study. The report, "Prevalence of Coronary Heart Disease in the Framingham Offspring Study: Role of Lipoprotein Changes," reproduced in abstract form earlier in this article, first appeared in the October 1980 issue of the *American Journal of Cardiology* (8). The cohort subjects consisted of the original 1,980 men and 2,421 women entered in the Framingham Heart Study between 1948 and 1951. The offspring subjects consisted of 1,719 men and 1,768 women—who were either genetic or adoptive offspring, or spouses of offspring of the original cohort. The HDL-C, an important variable not previously measured in many of the cohort group, and body weight and estimates of obesity were included. A greater proportion of younger men and women were represented in the offspring group. Of the men, 43 had clinically recognized CHD at enrollment, as did 11 of the women. The crude rate of clinical CHD (per 1,000) for the offspring slightly exceeded that of the cohort—25 versus 18 for men and 7 versus 6 for women. As in the cohort study, the prevalence of CHD was strongly associated with age, gender, smoking, systolic blood pressure and total cholesterol (T-C) and low-density lipoprotein cholesterol (LDL-C) levels, thus validating the prior conclusions. In addition, a decreased level of HDL-C, especially in women, and an increased T-C/HDL-C ratio were also found to be strongly associated with increased risk. Interestingly, the level of very low-density lipoprotein cholesterol (VLDL-C) did not prove to be an independent risk.

The finding of several risk factors in an individual subject was of particular significance in regard to overall or total individual risk for an adverse vascular event. The 12-year incidence of CHD in the Framingham offspring was reported in 1991 (9). Over the 12 years, 156 of the 1,663 men and 55 of the 1,714 women developed clinical CHD. Once again, CHD was significantly associated with age, gender, LDL-C levels, lower HDL-C levels and number of cigarettes smoked. Fasting glucose and LDL-C levels were highly associated with CHD in men but were borderline in women, whereas triglyceride and VLDL-C levels were not significantly associated with CHD after adjustment for HDL-C and blood glucose. Remarkably, a statistically significant association between systolic blood pressure and coronary artery disease (CAD) was not demonstrated in either men or women. Hypertension control had increased, cigarette smoking had declined during the 1970s and 1980s and the potential for large reductions in blood cholesterol

levels was evident. The longitudinal aspect of the study of CHD events again underscored the importance of lipids and fostered programs to optimize both T-C and LDL-C levels.

Epidemiology as a science basic to atherosclerosis and CAD. Although most reports concerning the Framingham Heart Study have appeared in general medical and epidemiologic journals, Dr. William B. Kannel's Bishop Lecture, "Contribution of the Framingham Study to Preventive Cardiology," published in the *Journal of the American College of Cardiology* in 1990 (10), amply justified the epidemiologic approach to the study of such a multifactorial disorder. Reliable, objective information was now available regarding the incidence of cardiovascular disease and the importance of risk factors in predicting the propensity for adverse clinical events.

Influence. This series of seminal reports (4-10) resulted in the establishment of the Lipid Research Clinic project (11) and the National Cholesterol Education Program (12,13), which have focused on the optimal management of atherosclerosis and CAD. The Framingham data have served many nations and remain the bedrock of programs worldwide. Unfortunately, control of lipids by diet alone has not proven satisfactory in U.S. patients (14,15). This finding has fostered the development of pharmaceuticals to effectively and safely reduce T-C and LDL-C (16). Prior concern regarding potential adverse clinical outcomes of lowered T-C has not been substantiated (17). Randomized clinical trials (RCTs) using drugs of the hepatic hydroxymethyl glutaryl coenzyme A (HMG Co-A) reductase-inhibitor class ("statins") have shown significant lowering of T-C and LDL-C to be associated with a striking reduction in CAD events in men and women following acute myocardial infarction (AMI) (18), men at greatly increased risk but without prior AMI (19), men and women with normal T-C levels post-AMI (20) and in a general population not at increased risk (21). However, RCTs serve only to distribute risk equally between enrolled test and control arms. Within each arm, the subjects are far from homogeneous, with individual risks ranging from negligible to inevitable. An RCT will demonstrate only an "average" outcome and whether any change between the means in placebo and treated groups is not due to chance alone. This "average" is due to a shift in the distribution of individual outcomes, and it is not illogical to postulate that this shift must occur in individuals within a cohort who are at greatest individual risk. Hence, clinical trial data must be reassessed with care to ensure that only those who can benefit receive treatment and that resources are not expended by "treating" persons who cannot benefit. Subpopulation analysis of risk is now critical, if for no other reason than to minimize inclusion of those at minimal risk for an adverse event.

The 27th Bethesda Conference of the American College of Cardiology (22), co-chaired by Drs. Thomas S. Pearson and Valentin Fuster, underscored the importance of "matching the intensity of treatment with the hazard for

CAD events." This principle is imperative because the cost of general application of statin therapy for all subjects at any level of risk would be prohibitive (23).

Dr. Peter Wilson has summarized the secular trends in cardiac risk factor levels from the Framingham experience (24). Mean systolic blood pressures were lower in the second-generation subjects, and the proportion of persons on blood pressure therapy increased in both sexes. Current cigarette smoking decreased, and there was only a slight increase in mean body mass levels. Whereas T-C and LDL-C levels were lower in the Framingham offspring, there was no significant difference between the cohort and the offspring groups in triglyceride and HDL-C levels. Although coronary death rates have declined greatly in the Framingham Study results and in the U.S. since 1970, a commensurate decrease in levels of coronary risk factors is less apparent. A significant part of this decline is due not to risk factor reduction but to treatment aimed at correcting a specific feature in an individual patient, i.e., the use of thrombolysis, coronary artery bypass graft (CABG) procedures and, more recently, coronary angioplasty with or without stent placement. Patients with any CHD events or cardiac symptoms now undergo careful scrutiny, and when secular risk factors are present (as they usually are), these patients are targeted for prompt and effective treatment. Again, the motivation of physicians and patients is strikingly different after such a wake-up call.

Overall risk estimation. It is now incontrovertible that blood pressure elevation, cigarette smoking, T-C levels and their subfractions and the presence of diabetes or insulin resistance combined with nonmodifiable factors of age and gender can provide in numerical terms a probability for CHD events over a follow-up interval of several years. A scoring sheet that allows physicians to estimate CHD risk has now been proposed (25). Although such estimates may be less than precise, they serve as excellent guidelines and may motivate patients at risk for CAD to adopt a healthy lifestyle and, when necessary, to receive appropriate medication. If, indeed, the intensity of management is to relate to the risk for coronary disease events, then a best numerical estimate of risk is an essential starting place.

I believe that such a risk score should be included in the chart of every patient; these scores would permit implementation of appropriate preventive strategies based on each patient's needs. For the future, it is reasonable to anticipate major additions to enhance the precision and utility of the Framingham risk estimate. Framingham fundamentally observed patients in a free-living environment. The management objective was, and is, primary prevention—namely, to hinder the development of non- or preclinical atherosclerotic disease and its complications. It is clear, however, that the Framingham risk factors play an even more important role in the management of existing coronary disease—designated as secondary prevention—where the 10-year risk is automatically doubled or quadrupled. To date, the most

cost-effective application of risk factor management has been in secondary prevention.

Accrual of carefully collected clinical detail about each patient, as well as the selected use of more advanced diagnostic techniques when required, can establish confidence in the degree of risk estimation needed for clinical decision making regarding treatment. Studies may include stress testing (with or without radionuclide or echocardiographic imaging), blood viscosity and white cell count, coronary calcification score, perhaps fibrinogen and homocysteine levels, and, in the future, identification of strong genetic markers. Addition of these variables will refine the accuracy of risk factor determinations and define more exactly for which individuals within a certain population specific therapy can be economically justified. Treatment defined on the basis of lipoproteins alone can be grossly misleading.

Impact of the Framingham Heart Study. Dr. Kannel's Bishop Lecture (10) summarized the contribution of the Framingham Heart Study to preventive cardiology. The association with frank diabetes or impaired glucose tolerance was greater in women but was also found to be highly dependent on coexisting cardiovascular risk factors, including lipid levels. Fibrinogen is another major and independent atherogenic risk factor that may be involved in both atherogenesis and thrombogenesis. The doubling of fibrinogen levels from the lowest to the highest may double the 12-year rate of CHD events. The Framingham study found a protective effect at low or moderate levels of exercise, dispelling the previously held opinion that it was necessary to exercise vigorously. Particularly in older individuals, exercise at a moderate level seemed to reduce the adverse CHD event rate by almost half over a 14-year interval. Although weight gain was found to make a modest independent contribution to CHD incidence, it, of course, promotes all of the other major atherogenic risk factors, including dyslipidemia, hypertension, impaired glucose tolerance, hyperglycemia and elevated fibrinogen; in addition, it is associated with a more sedentary lifestyle. In Dr. Kannel's 1994 report (26), "Clinical Misconceptions Dispelled by Epidemiological Research," he proposed that, even with current knowledge, a cardiovascular event must be regarded as a medical failure rather than the first indication of a treatment need. In most chronic congestive heart failure (CHF) patients, the primary causes of CHF are hypertension and ischemic heart disease. The incidence of CHF seems to be increasing, coincident with increased immediate survival after AMI as a consequence of newer therapies, including thrombolysis and primary angioplasty. The CHF outcomes remain unsatisfactory in terms of morbidity and mortality and now represent a great personal and economic burden on the individual and on society. Because revascularization does not decrease the incidence of AMI (27), lipid lowering with this purpose in mind is an idea whose time for testing has come. Epidemiologic studies have demonstrated

the relationship between peripheral arterial disease (PAD) and cardiovascular disease. Not unexpectedly, CHD is the most common immediate cause of death in PAD patients. The same primary risk factors associated with CHD also predict intermittent claudication and include systolic blood pressure level, presence of diabetes, cigarette smoking, elevated cholesterol and left ventricular hypertrophy. In PAD, the most powerful risk factors are cigarette smoking and diabetes.

Some, now mindful of the potentially dramatic changes in management that have been suggested by new findings on the fundamental processes of atherosclerosis, might debate Dr. Kannel's statement, "Epidemiology has emerged as the basic science for preventive cardiology" (26). However, the significant progress that has been attained to date in the management of vascular diseases is, nonetheless, based on the insights provided by the Framingham Heart Study investigators.

In spite of current trends toward, and increasing general dependence on, drug therapy, as well as lack of confidence in the U.S. in dietary approaches alone (19), recent data from eastern Finland (28) suggest that programs of community education and the availability of low-fat food have caused a significant reduction in lipoprotein risk factors. This Finnish study underscores the importance of cost considerations in the widespread application of all new strategies. Therapy for all patients at any risk with statins is cost prohibitive, even in the so-called developed countries.

CONCLUSIONS

The initiation of the Framingham Heart Study and the offspring study were true milestones in the history of cardiology—a conceptual leap forward. The resulting reports have provided a fundamental approach to the management of atherosclerotic disease. We who are involved in clinical care and clinical decision-making for individual patients will forever remain in debt to the many outstanding and dedicated scientists responsible for the purposeful design, effective data collection and responsible interpretation of the secular factors that underlie atherosclerotic vascular diseases.

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